deleted material is in brackets and the inserted material is underlined is attached hereto as **Exhibit A**:

C1

--55. (Amended) The method of claim 41, wherein the cell is a mononuclear phagocyte.--

**REMARKS**

Claims 1-26 and 34-58 were pending in the subject application. Applicants have hereinabove canceled claims 1-26, 34-40, 42, 43, 45 and 47-54 without prejudice or disclaimer to applicants right to pursue the subject matter of these claims in a later-filed application and amended claim 55. Support for this amendments may be found inter alia in the specification as follows: Claim 55: page 25, lines 27-31. Claim 55 does not involve any issue of new matter. Therefore, entry of this amendment is respectfully requested such that claims 41, 44, 46 and 55-58 will be pending.

Detaild Action:

The Examiner stated that the amendment filed 23 January 2002 (Paper No. 10) has been entered. The Examiner stated that claims 30-33 were canceled by the Applicant. The Examiner stated that claims 1-26,34-40,42,43,45 and 47-54 were withdrawn by the examiner. The Examiner stated that the text of those sections of the Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections and/or Rejections:

The Examiner stated that the objection to Claim 30 as recited in the previous Office Action (5 July, 2001; p.3) for depending from a canceled claim is withdrawn in that claim 30 has been canceled

(paper 10,23 January 2002). The Examiner stated that the rejection of claims 41,44,46,55 and 56 under 35 U.S.C. 103 (a) as recited in the previous Office Action (5 July, 2001; p.3-5), is withdrawn in light of the explanations by Applicant and the new 35 U.S.C. §103 (a) rejection, is discussed below.

Objection to the Figures:

The Examiner stated that the objections to the Figures as recited in the previous office action (July 5, 2001; p.3)- is maintained. The Examiner stated that applicants have indicated that they will submit formal drawings in the event there are allowable claims.

Objection to claims 45 and 55:

The Examiner stated that the objection to claims 45 and 55 is maintained because they allegedly recite or encompass non-elected inventions (See July 5, 2001 Office Action Summary; p.3).

Claim 45:

In response, applicants respectfully traverse the Examiner's objection to claim 45. Applicants maintain that 37 C.F.R. §1.141 provides that a reasonable number of species may still be claimed in one application provided the application also includes an allowable claim generic to all the claimed species and all the claims to species in excess of one are written in dependent form.

Applicants contend that an amyloid-β peptide selected from the group consisting of Aβ (1-39), Aβ (1-40), Aβ (1-42) and Aβ(1-40) Dutch variant are all peptides capable of forming amyloid and encompass a reasonable number of elected species written in dependent form as specified under 37 C.F.R. §1.141. Accordingly,

applicants respectfully request that the Examiner reconsider and examine claim 45.

Applicants contend that these comments obviate the Examiner's above objection. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of objection.

Claim 55:

Applicants respectfully traverse the Examiner's objection to claim 55. Nevertheless, without conceding the correctness of the Examiner's position, applicants have hereinabove amended claim 55 as follows: amended claim 55 recites "the method of claim 41, wherein the cell is a mononuclear phagocyte." Therefore, claim 55 no longer recites the alleged limitation "endothelial cell, a smooth muscle cell, a somatic cell, a bone marrow cell, a liver cell, an intestinal cell, a germ cell, a myocyte, a tumor cell, a spleen cell or a stem cell."

Applicants contend that this amendment obviates the Examiner's above objection. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of objection.

Information Disclosure Statement:

The Examiner stated that the listing of references in the specification is not a proper Information Disclosure Statement, and is therefore not of record. 37 C.F.R. §1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

In response, applicants respectfully point-out that the previously filed Amendment in Response to July 5, 2001 Office Action and Petition for a Three-Month Extension of Time did not include an Information Disclosure Statement for the Examiner's consideration. However, applicants respectfully direct the Examiner to the July 5, 2001 Office Action Summary which recites that "the Information Disclosure Statement received 12/29/99 (Paper 4) has been entered into the record." Therefore, while the applicants did not file an Information Disclosure Statement as part of the January 7, 2002 response, an Information Disclosure Statement received by the Examiner on December 29, 1999 was considered and entered into the record.

In addition, applicants respectfully note that in the April 9, 2002 Office Action Summary, the Examiner did not recite consideration of applicants Supplemental Information Disclosure Statement, Exhibit A (form PTO-1449), Exhibits 1-4 (Copy of references), and Exhibit B (Copy of International Search Report), filed on September 21, 2001 in connection with the above-identified application. Accordingly, applicants respectfully request that the Examiner consider and make of record this timely filed Supplemental Information Disclosure Statement including Exhibit A (form PTO-1449), Exhibits 1-4 (Copy of references), and Exhibit B (Copy of International Search Report).

Applicants contend that this response obviates the Examiner's above objection. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of objection.

Rejection under 35 U.S.C. §112, first paragraph:

The Examiner stated that the rejection of claims 41, 44, 46 and 55-56 under 35 U.S.C §112 is maintained for the reasons recited in the previous Office Action (5 July,2001; p.5-7). The Examiner alleged that the specification discloses using the soluble form of the receptor to inhibit binding of amyloid to RAGE in PC12 cells transfected with RAGE. The Examiner alleged that the disclosure also describes using the methods of the invention to inhibit binding of amyloid to splenic cells of mice, as measured by changes in NfkB, for example. The Examiner alleged that there is no link described in the disclosure that would enable the methods of treating a subject or disease *in vivo* as applicable to humans. The Examiner alleged that the applicants' arguments primarily center on "common denominators of fibrillar pathologies" (Specification, page 80, for example). The Examiner alleged that the applicant has argued that use of sRAGE to block peripheral amyloidosis in a mouse model is an example of an enabling in vivo use (Paper 10,23 January 2002, p.16). The Examiner alleged that the applicant also argued that accumulation of amyloid in the spleens of mice, the association of increased amyloid with IL-6 production (p 21), and its blockade by administration of sRAGE in a dose-dependent manner, are evidence that the methods described in the instant Specification can be applied to the increased amyloidosis associated with Alzheimer's disease. The Examiner alleged that a paper by Schenck, et al (1999,Nature,400:173) similarly stresses treatments aimed at reducing amyloid in a transgenic model of Alzheimer's disease. The Examiner alleged that the Picciotto, et al paper (1998, Physio. Rev. 78:1131) was submitted by the Applicant to support the argument that mice models of Alzheimer's disease are relevant and enabling for the claimed Invention. The Examiner alleged that applicants point to studies that administered

cyclo-oxygenase inhibitors to mice and humans as presumed evidence of the similarity between Alzheimer's disease and the transgenic mouse of amyloidosis (Wegen, et al,2001, Nature 414:212) and discuss evidence from the instant specification that administration of SRAGE dose-dependently suppressed splenic amyloid burden (p.21). The Examiner stated that the applicant's arguments (paper 10,23 January 2002) have been fully considered but are not deemed to be persuasive for the following reasons: The Examiner alleged that in support of their arguments that mice models of AD are relevant and enabling for the methods of the Instant Application, Applicants submitted the papers by Hsaio, et al and Picciotto, et al. The Examiner alleged that Hsaio's group produced transgenic mice which appear to produce abnormally high β-amyloid. The Examiner alleged that Picciotto, et al discuss that there are now several transgenic strains of mice demonstrating increased amyloid burden. The Examiner alleged that the brains of the transgenic mice in Hsaio's paper and several other studies have demonstrated plaques. The Examiner alleged that the amyloid over-producing transgenic mice of Hsaio's group showed a delayed syndrome of impaired learning and cerebral plaques (p.99). The Examiner stated that applicants submit that these mouse models adequately represent a human model of amyloidosis, namely Alzheimer's disease using the methods of the current invention. The Examiner alleged that applicants also point to the commentary by Hardy (1997, PNAS, 94:2095) which discusses amyloid deposition as involved or causative of disease ranging from faulty egg laying in nematodes to Alzheimer's disease and Down syndrome in humans. The Examiner alleged that there exist several problems with using mouse models of Alzheimer's disease in which there are defects in amyloid processing whether a therapy in humans will be effective. The Examiner alleged that as the Hsaio study

points out (p.99), Alzheimer's disease is a disease of unknown etiology, and cognitive deficits do not necessarily correlate well with amyloid deposition (first paragraph). The Examiner alleged that tests of learning and memory in animals cannot be seen to reflect the cognitive deficits seen in humans with Alzheimer's disease. The Examiner alleged that the experiments cited by the applicant utilize a simple maze to test the animals' memory or a swimming test. The Examiner alleged that many factors can contribute to the results obtained from such studies: sedation, reduction of motivation (e.g., satiety), or motor impairments, to name few. The Examiner alleged that "higher" motor functions, such as use of language and associative learning, are comprised early in the etiology of AD and in fact, are the defining deficits in the disease (Pearlman, et al, eds, Neurobiology of Disease, p.311). The Examiner alleged that such deficits that distinguish Alzheimer's diseases from other amyloid disease or from more localized causes of cerebral damage (i.e,stroke) cannot be adequately evaluated by means of an animal model. The Examiner stated that it should be noted that the papers submitted with the applicants' response are silent as to the possible contribution of AGE receptor to both the pathogenesis of amyloidosis and Alzheimer's disease, thus are allegedly poorly predictive of a method of treatment involving RAGE OR sRAGE.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the specification is enabled for a method of inhibiting binding of β-sheet fibril to RAGE on the surface of a cell located outside of the central nervous system. Applicants contend that the specification recites both *in vitro* and *in vivo* experimental data that demonstrate the inhibition of the

binding of β-sheet fibril to RAGE on the surface of a cell located outside of the central nervous system.

*In vitro* data:

The *in vitro* data demonstrate that RAGE interacts specifically with Aβ fibrils and that the blockade of RAGE completely suppressed symptoms of cellular stress such as fibril-dependent NF-κB activation and DNA fragmentation. The specification recites data that demonstrates that in a purified *in vitro* system, RAGE interacts specifically with Aβ fibrils while a peptide containing the reverse sequence of Aβ did not bind RAGE, nor did several other control peptides of hydrophobicity similar to Aβ. See page 63, lines 18-35 and page 64, lines 1-6. In order to relate RAGE engagement by amyloid fibrils to events occurring at the cell surface and their consequences for cellular behavior, the specification recites that stably-transfected PC12 cell-RAGE transfectants (PC12/RAGE) that overexpress wild-type receptor displayed increased total RAGE antigen by immunoblotting and elevated levels of cell surface RAGE by immunohistochemistry and increased MAP kinase pathway and NF-κB activation by ERK ½ immunoblotting. See page 67, lines 14-35 and page 68, lines 1-22. Further the specification recites that blockade of RAGE suppressed fibril-dependent NF-κB activation and DNA fragmentation completely. See page 72, lines 22-25. Therefore, the *in vitro* data demonstrate that RAGE interacts specifically with Aβ fibrils and that the blockade of RAGE completely suppressed symptoms of cellular stress such as fibril-dependent NF-κB activation and DNA fragmentation.

*In vivo* data

In a murine model of systemic amyloidosis, the *in vivo*

administration of sRAGE blocked amyloid fibril-RAGE interactions and suppressed cellular stress and amyloid fibril accumulation in mouse tissues. The specification recites as follows: "In a model of systemic amyloidosis, blockade of fibril-RAGE interaction *in vivo* suppressed cellular stress and amyloid A fibril accumulation." See page 57, lines 17-20. Further, the specification recites that in an *in vivo* model of systemic amyloidosis, blockade of fibril-RAGE interaction suppressed cellular stress and amyloid A fibril accumulation, suggesting that cell surface RAGE is a focal point for interaction with fibrils, which renders amyloid pathogenic by a receptor-dependent mechanism. See page 74, lines 1-31. Therefore, the specification teaches that in a mouse model of systemic amyloidosis, the ***in vivo*** **administration of sRAGE blocked amyloid fibril-RAGE interactions and suppressed cellular stress and amyloid A fibril accumulation in tissues.** Accordingly, applicants contend that the specification is enabled for a method of inhibiting binding of β-sheet fibril to RAGE on the surface of a cell located outside of the central nervous system.

Applicants contend that these comments obviate the Examiner's above rejection and respectfully request that the Examiner reconsider and withdraw this rejection.

Rejection of claims 57-58 under 35 U.S.C. §112, first paragraph:
The Examiner maintained the rejection of claims 57 and 58 under U.S.C. 112, first paragraph, as recited in the previous Office Action (5 July,2001; p.5-7). The Examiner alleged that the claims of the present invention read on using sRAGE to inhibit binding of ligand and thus modulate a disease state involving β-sheet fibrils. The Examiner alleged that the specification discloses using the

soluble form of the receptor to inhibit binding of amyloid to RAGE in PC12 cells transfected with RAGE. The Examiner alleged that the disclosure also describes using the methods of the invention to inhibit binding of amyloid to splenic cells of mice, as measured by changes in NfkB, for example. The Examiner alleged that there is no nexus described in the disclosure that would enable the methods of the invention as applied to Alzheimer's disease or to inhibiting binding of ligand to RAGE in a diseased subject. The Examiner stressed the complexity of Alzheimer's disease and the involvement, for example, of many types of proteins in plaque formation, besides β-amyloid. The Examiner alleged that the applicant has argued that use of sRAGE to specifically block amyloid formation in vitro, as well as the fact that one could use in vitro data together with in vivo data in the literature, as a whole demonstrate the ability of the disclosed invention to modulate a disease state. The Examiner alleged that the applicant argues that the specification discloses "common denominators of fibrillar pathologies" (specification, page 80). The Examiner alleged that no data is referred to in the specification or in the literature that demonstrates the processes described and claimed as pertaining to Alzheimer's disease, or to use in subjects, for example. The Examiner alleged that there is no evidence presented of the chain of events that presumably links amyloid to Alzheimer's disease by means of RAGE. The Examiner alleged that using the methods of the invention to inhibit binding of amyloid to transfected cells or splenic cells of mice, as measured by changes in NFkB, for example, is not shown to be further linked to preventing a disease process.

In response, applicants respectfully traverse the Examiner's rejection. Applicants contend that the specification is enabled

for a method of inhibiting the binding of β-sheet fibril to RAGE using sRAGE. Applicants contend that the specification recites *in vivo* experimental data that demonstrates the inhibition of the binding of amyloid fibril to RAGE by sRAGE.

In a murine model of systemic amyloidosis, blockade of fibril-RAGE interactions with sRAGE *in vivo* suppressed cellular stress and amyloid fibril accumulation in tissues. The specification recites as follows: "In a model of systemic amyloidosis, blockade of fibril-RAGE interaction *in vivo* suppressed cellular stress and amyloid A fibril accumulation." See page 57, lines 17-20. Further, the specification recites that in an *in vivo* model of systemic amyloidosis, blockade of fibril-RAGE interaction suppressed cellular stress and amyloid A fibril accumulation, suggesting that cell surface RAGE is a focal point for interaction with fibrils, which renders amyloid pathogenic by a receptor-dependent mechanism. See page 74, lines 1-31. Therefore, the specification teaches that in a mouse model of systemic amyloidosis, the ***in vivo*** **administration of sRAGE blocked amyloid fibril-RAGE interactions** and suppressed cellular stress and amyloid A fibril accumulation in tissues. Accordingly, applicants contend that the presently claimed invention is enabled.

Applicants contend that these comments obviate the Examiner's above rejection and respectfully request that the Examiner reconsider and withdraw this rejection.

Rejection Under 35 U.S.C. §103(a):

The Examiner rejected claims 41, 44, 46 and 55-58 under 35 U.S.C. §103(a) as being unpatentable over Miyata et al.(1997, PNAS,

94:5296) further in view of Yan et al. (PNAS, 1997, 94: 5296). The Examiner stated that as alluded to by the Applicant (5 July 2001, p.6), it is possible that cell-type or location may be important in distinguishing the invention of the instant application from similar methods in the receptor field. The Examiner alleged that evidence of prior art should therefore reflect the type of cell used for the relevant experiments as well as the methods. The Examiner alleged that the instant specification discloses using the soluble form of the receptor to inhibit binding of amyloid to RAGE in PC12 cells transfected with RAGE or in splenic cells or mononuclear phagocytes. The Examiner alleged that the disclosure also describes using the methods of the invention to inhibit binding of amyloid to splenic cells of mice, as measured by changes in NfkB, for example. The Examiner alleged that Miyata et al. discuss the presence of RAGE in mononuclear phagocytes (Miyata, et al, 1996, J. Clin. Invest., 98:1088). The Examiner alleged that Miyata et al. state that this may be significant because the AGE ligand AGE-β2M (amyloid), by interacting with RAGE on mononuclear phagocytes, may contribute to the damage of peripheral tissues in long term hemodialysis patients. The Examiner alleged that Miyata et al. demonstrated specific binding of AGE ligand to MPS, dose-dependent transduction processes, and inhibition of AGE ligand binding using a specific antibody to RAGE (see, Fig. 1). The Examiner stated that Miyata, et al, did not measure oxidative damage directly after exposure of RAGE-containing cells to ligand. The Examiner alleged that they did, however, measure cell chemotaxis, and in fact, blocked that process using the soluble from of the RAGE receptor. The Examiner alleged that Miyata et al. did provide a strong indication that cellular damage could be triggered by RAGE ligand in their use of N-acetylcysteine to

inhibit indicators of oxidative stress (Figure 4). The Examiner alleged that Yan et al. teaches binding of a β-sheet fibril, namely Amyloid-β, to the RAGE receptor on microglia. The Examiner alleged that Yan et al. further measure the resultant oxidative stress reaction triggered by activation of RAGE on those cells. The Examiner alleged that measurements of oxidative stress included measurement of inflammatory pathways involving transcriiption factor NFkB. The Examiner alleged that Yan et al. suggest that these processes may contribute to the cellular pathologies seen in Alzheimer's disease. The Examiner stated that Yan et al. do not teach inhibition of binding of β-sheet fibril to RAGE. The Examiner stated that since Yan et al. did not teach inhibition of this binding event, or especially, inhibition using a soluble receptor, and since Miyata's group did not teach evidence of oxidative damage, the teachings of Miyata et al. and Yan et al. were combined to render the instant invention obvious. The Examiner alleged that as binding of a ligand to RAGE triggers a cascade of events leading to oxidative damage (e.g., Yan et al.), and because Miyata et al. use soluble receptors to compete for ligand binding, it would be obvious to someone skilled in the art to use sRAGE in the manner described in the instant application to inhibit ligand binding. The Examiner stated that claims 41, 44, 46, 55, 56, 57 and 58 are rejected for the reasons cited above.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that Miyata et al. is not available as a prior art reference against the presently claimed invention.

In support, applicants respectfully direct the Examiner to the May 11, 2001 Amendment in Reply to March 26, 2001 Office Action and

Petition for a One-Month Extension of Time filed with the United States Patent and Trademark Office in connection with the above-identified application which recites as follows:

"On page 1, line 5, please insert the following paragraph:

This application claims priority of U.S. Serial No. 08/592,070, filed January 26, 1996 and of U.S. Serial No. 08/948,131, filed October 9, 1997 under 35 U.S.C. §120, the contents of which are hereby incorporated by reference into the present application."

Therefore, applicants claim of priority under 35 U.S.C. §120 to U.S. Serial No. 08/592,070, filed January 26, 1996, antedates the Examiner's prior art reference, i.e. Miyata et al.(1997, PNAS, 94:5296). Therefore, applicants contend that Miyata et al. is not available as a prior art reference against the presently claimed invention.

Applicants contend that these comments obviate the Examiner's above rejection and respectfully request that the Examiner reconsider and withdraw this rejection.

Summary:

For the reasons set forth hereinabove, applicants respectfully quest that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims, i.e. claims 2-5.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned

attorney invites the Examiner to telephone at the number provided below.

No fee, is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

7/9/02

John P. White Date
Reg. No. 28,678

John P. White
Registration No. 28,678
Attorney for Applicant(s)
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

**Exhibit A:**

--55. (Amended) The method of claim 41, wherein the cell is [an endothelial cell, a smooth muscle cell, a somatic cell, a bone marrow cell, a liver cell, an intestinal cell, a germ cell, a myocyte,] a mononuclear phagocyte[, a tumor cell, a spleen cell or a stem cell].--